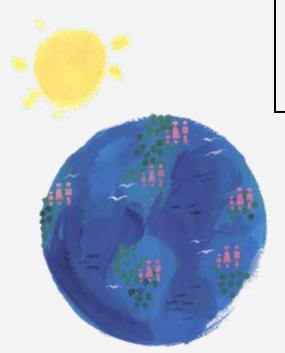
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ICCVAM

National Toxicology Program
Interagency Center for the Evaluation of
Alternative Toxicological Methods

Interagency Coordinating Committee on the Validation of Alternative Methods



NICEATM-ICCVAM Update

William S. Stokes, D.V.M, D.A.C.L.A.M. RADM, U.S. Public Health Service Executive Director, ICCVAM Director, NICEATM

Meeting of the Scientific Advisory Committee on Alternative Toxicological Methods June 18-19, 2008 Research Triangle Park, NC











Acknowledgements: Interagency Coordinating Committee on the Validation of Alternative Methods

Consumer Product Safety Commission

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Environmental Protection Agency

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Office of Research and Development • Julian Preston, Ph.D

-Suzanne McMaster, Ph.D.

OECD Test Guidelines Program

-Jerry Smrchek, Ph.D.

Office of Pesticides Programs

-Amy Rispin, Ph.D.

-Deborah McCall

Agency for Toxic Substances and Disease Registry

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Center for Devices and Radiological Health

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Center for Biologics Evaluation and Research

-Richard McFarland, Ph.D., M.D.

-Ying Huang, Ph.D.

Center for Food Safety and Nutrition

-David G. Hattan, Ph.D.

-Robert L. Bronaugh, Ph.D.

Center for Veterinary Medicine

-Devaraya Jagannath, Ph.D.

-M. Cecilia Aguila, D.V.M.

National Center for Toxicological Research

-William T. Allaben, Ph.D.

-Paul Howard, Ph.D.

Office of Regulatory Affairs

-Laurence A. D'Hoostelaere, Ph.D.

National Library of Medicine

ΦJeanne Goshorn, M.S.

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Acknowledgements: NICEATM

NIEHS

William S. Stokes, D.V.M., D.A.C.L.A.M. Director; Project Officer

Raymond Tice, Ph.D. Deputy Director

Debbie McCarley Special Assistant; Asst. Project Officer

On-site Center Support Contract (ILS, Inc.)

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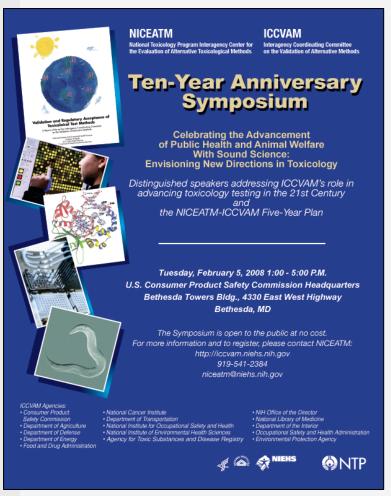
Outline

- Ten-Year Anniversary Symposium
- NICEATM-ICCVAM Five-Year Plan
- International Cooperation on Alternative Test Methods
- Ocular Safety Assessments
- Acute Systemic Toxicity
- Allergic Contact Dermatitis Assays
- Biologics Testing
- Endocrine Disruptor Assays
- Genetic Toxicity Assays
- Dermal Safety Assessment Assays
- Outreach Activities



NICEATM-ICCVAM Ten-Year Anniversary Symposium

Celebrating the Advancement of Public Health and Animal Welfare with Sound Science: Envisioning New Directions in Toxicology



- February 5, 2008
- CPSC Headquarters, Bethesda, MD
- Over 100 attendees
- Speakers from Federal agencies, academe, industry, and animal protection
- NICEATM-ICCVAM Five-Year
 Plan released



NICEATM-ICCVAM Ten-Year Anniversary Symposium



Featured speakers:

- Samuel Wilson, M.D.
 Acting Director, NIEHS and NTP
- Bernard Schwetz, D.V.M, Ph.D.
 Former Director
 DHHS Office for Human Research
 Protections
- Martin Stephens, Ph.D.
 Vice President for Animal Research Issues
 Humane Society of the United States
- Daniel Krewski, Ph.D.
 Director, McLaughlin Center for Population Health Risk Assessment University of Ottawa
- John Bucher, Ph.D.
 Associate Director, NTP
- Harold Zenick, Ph.D.
 Director
 National Health and Environmental Effects
 Laboratory, EPA
- Janet Woodcock, M.D.
 Deputy Commissioner and Chief Medical Officer, FDA



NICEATM-ICCVAM Ten-Year Anniversary Symposium



- Panel discussants from:
 - Government
 - Industry
 - Academe
 - Animal protection
 - SACATM
 - Europe and Japan counterparts
 - ECVAM
 - JaCVAM
 - NTP ExecutiveCommittee



ICCVAM: The First Ten Years

- 17 alternative methods accepted or endorsed by U.S. regulatory agencies since 1999
 - 12 non-animal methods
 - 10 based on ICCVAM technical evaluations
 - Impact: Includes 3Rs alternatives for the four most commonly performed product safety tests
- Recommendations for R&D, translation, and validation activities
- International guidance
 - Validation and acceptance
 - GLPs and in vitro testing
- Performance standards
 - To expedite validation and regulatory acceptance
- International partnerships: ECVAM & JaCVAM





NICEATM-ICCVAM Five-Year Plan



- Forwarded to House and Senate Appropriation Committees
 - February 4, 2008 by DHHS
- Copies released at the Ten-Year Anniversary Symposium
 - NIEHS press release
- Emphasizes
 - Priority areas for the 3Rs
 - Application of new science and technology
 - Partnerships
 - International cooperation and harmonization



International Cooperation on Alternative Test Methods

Purpose: To promote *consistent* international cooperation, collaboration, and communication among national validation organizations (ICCVAM-NICEATM, ECVAM, JaCVAM, Health Canada) in order to:

- Ensure optimal design and conduct of validation studies
 - To support national and international regulatory decisions on alternative methods proposed for regulatory testing.
- Ensure high quality independent scientific peer reviews
 - That provide for transparency and broad opportunity for stakeholder involvement
- Enhance likelihood of harmonized recommendations by national validation organizations
 - More rapid international adoption of alternative methods
- Leverage limited resources to achieve greater efficiency and effectiveness; avoid duplication of effort

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Alternative Methods for Ocular Safety Assessments

NIH Publication No. 07-4517. ICCVAM TEST METHOD EVALUATION REPORT In Vitro Ocular Toxicity Test Methods for Identifying Severe Irritants and Corrosives Interagency Coordinating Committee on the Valleation of Alternative Methods (ICCVAM). National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) National Institute of Environmental Health Sciences Vational Institutes of Health U.S. P. blz Heath Service epartment of Health and Human Services

- ICCVAM recommendations on four alternative methods transmitted to agencies in October, 2007
- ICCVAM Test Method Evaluation Report: In Vitro Ocular Toxicity Test Methods for Identifying Severe Irritants and Corrosives
 - Two methods, BCOP and ICE Assays, considered useful for regulatory hazard classification testing
 - When used in a tiered-testing strategy, positive substances can be classified as ocular corrosives or severe irritants without the need for animal testing
- Recommendations accepted or endorsed by all applicable agencies
- More details in next agenda item



Alternative Methods for Ocular Safety Assessments: Current & Planned Activities-1

- Evaluate Improvements to the BCOP and ICE Test Methods
 - To improve accuracy for identifying substances that cause permanent or severe eye damage: "top-down" approach
 - Essential for a non-animal approach for ocular safety testing
 - Planned activities:
 - Evaluate BCOP alternative corneal holder
 - Develop guidance and decision criteria for histopathology assessments
- Evaluate in vitro test methods to identify substances that cause reversible or no eye damage
 - Prepare background review documents and conduct independent peer review
 - Coordinated with ECVAM and JaCVAM
 - BCOP,ICE, IRE, and HET-CAM: ICCVAM-NICEATM lead
 - Florescein Leakage, Neutral Red Release, Cytosensor Microphysiometer: ECVAM lead
 - Two human reconstituted tissue models: COLIPA/ECVAM lead

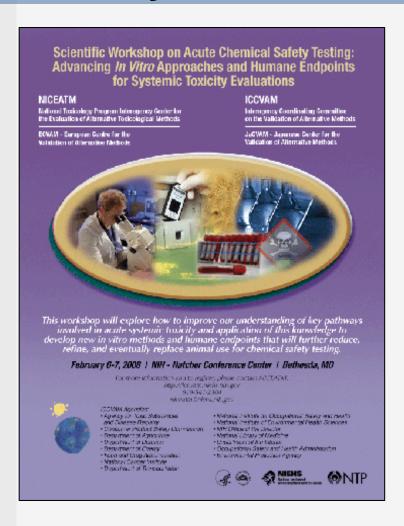


Alternative Methods for Ocular Safety Assessments: Current & Planned Activities-2

- Assess integrated decision strategies using data from multiple methods and biological activity information
 - Priority: Assess strategies for identifying non-irritant/non-corrosive substances
 - "Bottom-up" approach
- Evaluate non-animal approach for determining ocular hazard potential of antimicrobial cleaning products (AMCPs)
 - Submitted in Jan 08 by the Institute for In Vitro Sciences, Inc. on behalf of several companies
 - Proposed test methods: BCOP, Epiocular, Cytosensor Microphysiometer
 - Currently awaiting additional validation information from sponsor
 - Independent Peer Review meeting TBA
- Comprehensive review of topical anesthetics and systemic analgesics
 - To reduce or alleviate potential pain and distress where animals must still be used
 - Determine if available data and information support routine rather than current optional use



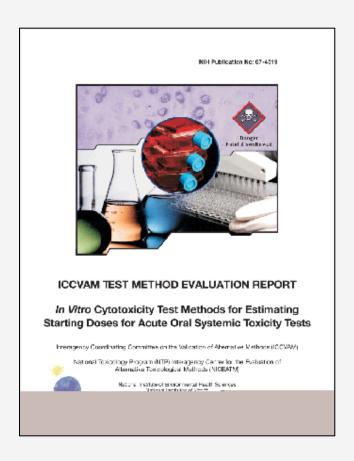
Alternative Methods for Acute Systemic Toxicity



- International Workshop on Acute Chemical Safety Testing
- February 6 and 7, 2008
 - Natcher Conference Center, NIH, Bethesda, MD
- Organized and sponsored by NICEATM, ICCVAM, ECVAM, and JaCVAM
- 120+ participants
- Workshop Goal
 - Determine how key in vivo toxicity pathway information can be collected and used to develop:
 - More predictive mechanism-based in vitro test systems
 - Earlier more humane endpoints for in vivo test methods
- Agenda item, Day 2



Alternative Methods for Acute Systemic Toxicity: ICCVAM Recommendations



- In Vitro Cytotoxicity Test Methods for Estimating Starting Doses for Acute Oral Systemic Toxicity Tests
- Based on joint NICEATM-ECVAM validation study
- Should be considered before using animals for acute oral toxicity testing
 - Provide for animal reduction and refinement
- More details in next agenda item



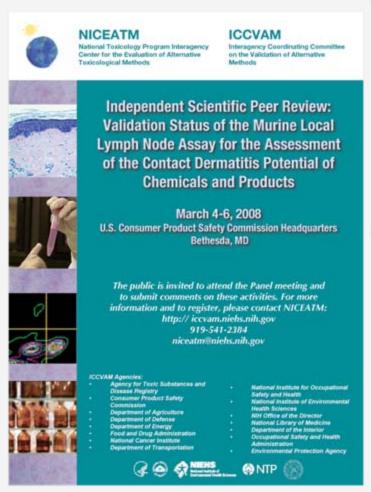
Alternative Methods for Acute Systemic Toxicity: Current & Planned Activities

- Implementation activities: Workshop recommendations
- Develop and evaluate an Up-and-Down Procedure for acute dermal systemic toxicity
 - Use computer simulations to model performance
- Assess reduction methods for acute inhalation toxicity

- Evaluate usefulness of the 3T3 NRU cytotoxicity test method for predicting starting doses for acute oral toxicity testing of mixtures
- Further evaluate in vitro limit dose to identify nontoxic substances



Alternative Methods for Allergic Contact Dermatitis



- Peer review meeting: March 4-6, 2008
 - CPSC Headquarters, Bethesda, MD
 - 20 international experts from eight countries
 - >50 attendees
- Evaluated modifications and new applications of the LLNA
 - 3 modified protocols that do not use radioactive materials
 - The limit dose procedure
 - Use of the LLNA for mixtures, aqueous solutions, and metals
 - Use of the LLNA for potency determination for hazard classification purposes

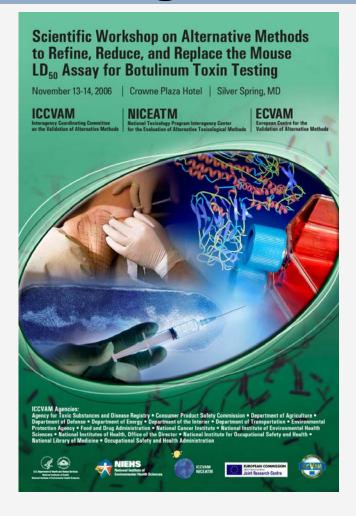


Alternative Methods for Allergic Contact Dermatitis: Current & Planned Activities

- Finalize Limit dose Procedure BRD and ICCVAM Test Method Evaluation Report
- Work to harmonize LLNA Performance Standards with ECVAM; publish final recommendations
- Request additional existing data, update BRDs and reconvene Peer Panel to further evaluate:
 - The 3 non-radioactive LLNA methods
 - The applicability domain of the LLNA
 - Use of the LLNA for potency determinations
- Update OECD Test Guideline 429: Skin Sensitisation: Local Lymph Node Assay



Alternative Methods for Biologics Testing



- Scientific Workshop on Alternative Methods to Refine, Reduce, and Replace the Mouse LD50 Assay for Botulinum Toxin Testing
- Co-sponsored by ICCVAM, NICEATM, and ECVAM
- Workshop Report available at
 - http://iccvam.niehs.nih.gov/
 - Review of the state-of-the-science and current knowledge of alternatives that may reduce, replace, and refine the use of mice for botulinum toxin testing
 - Priorities for research, development, and validation efforts needed to advance the use of alternative methods



Alternative Methods for Biologics Testing: Current & Planned Activities

- Evaluate alternatives for vaccine potency testing
 - Awaiting completion of USDA studies on an alternative method for potency testing of veterinary vaccines for Leptospirosis



Alternative Testing Methods for Endocrine Disruptors: Current & Planned Activities

- **International Validation Study of the LUMI-CELL® Estrogen Receptor Transcriptional Activation Assay¹**
 - Organized by NICEATM, ECVAM, and JaCVAM
 - Three labs: US, ECVAM, and Japan; 78 chemicals
 - Phase I of 4 complete; Phase 2 in progress
 - Independent Scientific Peer Review: 2009
 - OECD Test Guideline proposal: 2009
 - Will include performance standards to expedite validation of similar ER TA methods

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¹ The LUMI-CELL® assay (® XDS, Inc.) is an in vitro estrogen receptor (ER) transcriptional activation (TA) assay based on an immortalized human ovarian adenocarcinoma cell line that endogenously express estrogen receptors and have been stably transfected with the plasmid pGudLuc7. Advancing Public Health and Animal Welfare

Alternative Methods for Genetic Toxicity Testing: Current & Planned Activities

- Draft OECD TG 487: In Vitro Micronucleus Assay
 - ICCVAM comments submitted to OECD via U.S. NC
 - GTWG members participated in the OECD Expert Consultation on the *In Vitro* Micronucleus Test (Oct. 2007)
 - GTWG continues to contribute to efforts to harmonize the approach for evaluating cytotoxicity
- Jacvam In Vivo Comet Assay Validation Study
 - GTWG comments provided on draft protocols and study design

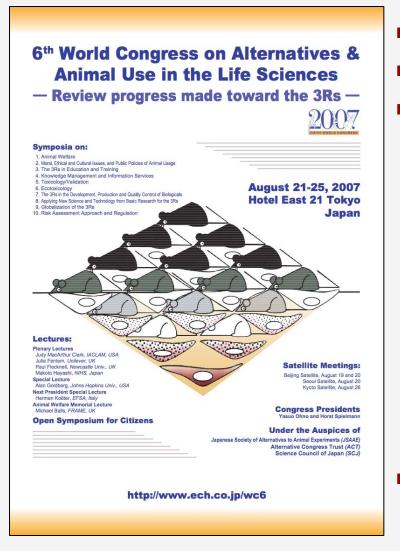


Alternative Methods for Dermal Safety Assessments: Current & Planned Activities

- EpiDerm[™] and EPISKIN[™] skin irritation assays
 - Study plan to determine how in vitro dermal irritation test methods (i.e., EpiDerm™ and EPISKIN™) will classify false negative chemicals from in vitro corrosivity test methods
 - Currently false negatives *in vitro* corrosivity assays: 12% to 21%
 - Confirm extent that identifying substances that directly reduce MTT (i.e., act as false negatives) will reduce false negative corrosive results
- Evaluate draft OECD Test Guideline for In Vitro Skin Irritation Assay
- Update OECD Test Guidelines to include Performance Standards (ICCVAM, 2004)
 - TG 430: In Vitro Skin Corrosion: Transcutaneous Electrical Resistance Test
 - TG 431: In Vitro Skin Corrosion: Human Skin Model Test



6th World Congress on Alternatives & Animal Use in the Life Sciences



- August 21-25, 2007, Tokyo, Japan
- Over 1000 attendees, 33 countries
- ICCVAM and NICEATM
 - 12 participants, 7 agencies
 - 23 presentations
 - 12 oral papers
 - 11 posters
 - Chaired 7 sessions
 - Organizing Committee: 2 members
 - Program Committee: 5 members
- 7th WC: Aug 30-Sept 4, 2009



2008 Society of Toxicology Meeting NICEATM-ICCVAM Presentations



Five Poster Presentations

- The NICEATM-ICCVAM Five Year Plan
- Performance characteristics of the LLNA Limit Dose Procedure
- ICCVAM recommendations on in vitro pyrogen test methods
- In vitro methods for estimating rat acute oral toxicity: prediction of GHS categories
- Alternative use of in vitro test data to determine when rat acute oral toxicity testing should start with the limit test

Abstracts and posters on the NICEATM-ICCVAM website

- http://iccvam.niehs.nih.gov/meetings/SOT08/sotablst.htm
- 2009 Meeting, March 15-19, 2009
 - Proposals for two workshops on alternative methods
 - Posters on recent progress



Thank you for your attention.

Questions?

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